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Human-Bovine Reassortant Rotavirus Vaccine

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Rotavirus is the most common cause of gastroenteritis worldwide. In the United States, rotavirus accounts for approximately 400,000 clinic visits, 200,000 emergency department visits, 55,000 to 70,000 hospitalizations, and 20 to 60 childhood deaths each year. After a 1 to 3 day incubation period, rotavirus illness typically begins with the abrupt onset of vomiting and diarrhea, often accompanied by fever. Symptoms generally resolve after 3 to 7 days. In severe cases, rotavirus infection can result in significant dehydration, electrolyte imbalance, and shock.¹

The first rotavirus vaccine available for use in the United States, Rotashield®, was approved in 1998. This product, a tetravalent rhesus-based vaccine, was withdrawn from the market less than a year after its introduction because of its association with intussusception. On February 3, 2006, the Food and Drug Administration (FDA) approved RotaTeq®, a new vaccine for the prevention of rotavirus gastroenteritis that appears to have an improved adverse effect profile.^{2,3} Last month, the Advisory Committee on Immunization Practices (ACIP) issued their recommendations on the use of rotavirus vaccine for routine immunization of infants and children in the United States.¹ This issue of *Pediatric Pharmacotherapy* will describe the new rotavirus vaccine and review the available studies documenting its efficacy and safety in children.

Vaccine Components

The RotaTeq® vaccine is a live, oral vaccine consisting of five human-bovine reassortant strains (G1, G2, G3, G4, and P[8]). Each dose of the vaccine contains approximately 2×10^6 infectious units of each reassortant strain in a buffered solution. The viral strains replicate in the small intestine and induce immunity. Seroconversion, defined as a 3-fold or greater rise in anti-rotavirus immunoglobulin A, has been demonstrated in 93 to 100% of subjects in clinical trials.²⁻⁴

Efficacy in Children

The primary data supporting the efficacy and safety of the rotavirus vaccine has come from the Rotavirus Efficacy and Safety Trial (REST), a randomized, double-blind, placebo-controlled trial involving 68,038 infants. The subjects were all between 6 and 12 weeks of age at enrollment and received three doses of vaccine at 4 to 10 week intervals. The infants were evaluated over a 42-day period for serious adverse events, including intussusception. Parents or guardians were also contacted every 6 weeks for one year to identify additional adverse effects.⁵

A total of 13 infants in the vaccine group were seen in an emergency department for G1-G4 rotavirus gastroenteritis, compared to 191 infants in the placebo group. Six vaccinated infants and 138 infants in the placebo group required hospitalization. The vaccine reduced the combined incidence of emergency department visits or hospitalizations resulting from G1-G4 rotavirus gastroenteritis by 94.5% (95% CI 91.2, 96.6). The incidence of hospitalizations for all gastroenteritis was reduced by 58.9% (95% CI 51.7, 65.0). The frequency of clinic or office visits for G1-G4 rotavirus gastroenteritis was reduced by 86% (95% CI 73.9, 92.5).⁵

In a nested substudy of 5,673 vaccinated infants, overall efficacy against G1-G4 rotavirus gastroenteritis was 74% (95% CI 66.8, 79.9) during the first full rotavirus season following immunization. Efficacy against severe gastroenteritis, as assessed by use of a standardized scale, was 98.0% (95% CI 88.3, 100).⁵

The manufacturer conducted a second study which has not been published. In this trial, a total of 650 infants received rotavirus vaccine and 660 were given placebo. There were 15 cases of gastroenteritis in the vaccine patients and 54 cases in the controls, including six severe cases, giving an efficacy estimate of 72.5% (95% CI 50.6, 85.6).⁵

Contraindications and Precautions

Rotavirus vaccine is contraindicated in patients with a known hypersensitivity to any component of the vaccine or in infants who have had hypersensitivity reactions with a previous dose of the vaccine. Vaccination should be postponed in patients with a febrile illness, but low-grade fever (less than 38.1° C) or mild upper respiratory tract infections are not considered contraindications to rotavirus vaccination. The vaccine should not be administered to infants with acute, moderate-to-severe gastroenteritis; however, it may be given to infants with mild gastroenteritis.^{2,3}

There are currently no data to determine the safety and efficacy of rotavirus vaccination in immunocompromised patients, including those with leukemia, lymphoma, or malignant neoplasms, infants receiving systemic immunosuppressive therapy, infants with immunodeficiency states, or those who have received blood products or immunoglobulins within the previous 42 days. There are also no data available on the use of the rotavirus vaccine in infants with chronic underlying gastrointestinal disorders or a history of intussusception.^{2,3}

Viral shedding has been demonstrated in the stool samples of 0.3-8.9% of patients receiving rotavirus vaccine. Shedding has been documented as early as 1 day after immunization and as late as 15 days after a dose. As a result, families should be aware of the potential risk to close contacts who are immunocompromised.^{2,3}

Drug Interactions

Immunosuppressive therapies, including antimetabolites, alkylating agents, cytotoxic drugs, and systemic corticosteroids, may reduce the immune response to rotavirus vaccine. The use of inhaled or topical corticosteroids does not appear to adversely affect response to the vaccine.^{2,3}

Adverse Effects

Information on the safety of rotavirus vaccine has been determined from the cumulative results of three clinical trials conducted in infants. The most commonly reported adverse events in these trials were irritability (4.3-7.1% in patients receiving vaccine compared to 4.5-7.1% with placebo), diarrhea (6.1-10.4% compared to 5.4-9.1% in placebo patients), vomiting (3.6-6.7% compared to 3.2-5.4% with placebo), and temperature greater than or equal to 38.1° C rectally (17.1-20% compared to 16.2-19.4% with placebo). Other reactions reported by parents included bronchospasm (1.1%), nasopharyngitis (6.9%), and otitis media (14.5%).^{2,3}

Subset analysis of preterm infants in the REST trial revealed a similar adverse reaction profile to that observed in older infants. Irritability was reported in 3-8% of infants, diarrhea in 4-7%, vomiting in 3-6%, and elevated temperature in 15-25%.⁴

Serious adverse reactions reported after rotavirus vaccine immunization have included bronchiolitis (0.6% in vaccine recipients compared to 0.7% in control subjects), gastroenteritis (0.2% versus 0.3% in controls), pneumonia (0.2% in both groups), fever (0.1% in both groups), and urinary tract infections (0.1% in both groups). The incidence of seizures was no different in the study infants given vaccine and those receiving placebo (less than 0.1%).^{2,3}

Cases of intussusception were monitored for 1 year after vaccine administration in the REST trial. At 42 days post-dose, there were 6 cases in the 34,837 vaccine recipients and 5 cases in the 34,788 placebo patients (relative risk 1.6, 95% CI 0.4, 6.4). At the end of one year, there were 12 cases in the vaccine group and 15 cases in the placebo group (relative risk 0.9, 95% CI 0.4, 1.9).⁵

Dosing

RotaTeq® is available as an oral suspension in 2 mL single-dose latex-free tubes. The vaccine must be kept refrigerated and protected from light until use. The manufacturer recommends that rotavirus vaccine be administered in a 3-dose series to infants between 6 and 32 weeks of age, with the first dose given when the patient is between 6 and 12 weeks of age. The ACIP recommends routine immunization at 2, 4, and 6 months of age. Premature infants may be immunized as early as 6 weeks postnatal age, if believed to be at increased risk for infection.^{2,3}

There is no need to restrict feeding prior to or after administration of rotavirus vaccine. The vaccine should not be diluted or mixed with any other liquids. It may be administered at the same time as diphtheria, tetanus, acellular pertussis vaccine, as well as inactivated poliovirus vaccine, *Haemophilus influenzae* type b conjugate vaccine, hepatitis B vaccine, or pneumococcal conjugate vaccine. The manufacturer has conducted studies to demonstrate the lack of interference of rotavirus vaccine on the immune response to all of these vaccines except pertussis, which is currently under review.^{2,3}

Because it contains live virus, the vaccine packaging should be discarded in approved biological waste containers.^{2,3}

Cost

RotaTeq[®] is manufactured by Merck. The average wholesale cost is \$83.88 per 2 mL dose.⁶ Rotavirus vaccine was approved for the Vaccines for Children program on February 22, 2006.⁷

Summary

Rotavirus vaccine is the newest addition to the routine childhood immunization schedule. While only limited information is available from clinical trials, the vaccine appears to be highly effective and well tolerated. In trials with follow-up at 1 year, the incidence of intussusception in infants receiving the vaccine has been no different than those given placebo. While this new vaccine appears to offer the promise of a significant decrease in a common childhood infectious disease, additional experience is needed to confirm its safety.

References

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2. Rotavirus vaccine, live. *Drug Facts and Comparisons*. Efacts [online]. 2006. Available from Wolters Kluwer Health, Inc. (accessed 8/19/06).
3. RotaTeq[®] prescribing information. Merck & Co., Inc., February 2006.
4. Clark HF, Offit PA, Plotkin SA, et al. The new pentavalent rotavirus vaccine composed of bovine strain (WC3)-human rotavirus reassortants. *Pediatr Infect Dis J* 2006;25:577-83.
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6. 2006 Red Book. Montvale, NJ. Medical Economics, 2006.
7. Vaccines for Children Program. Available at www.cdc.gov/nip/vfc/default.htm (accessed 8/19/06).

Pharmacology Literature Review

* **Note to readers:** The URL for the bioterrorism emergency dosing cards was printed incorrectly in the last issue. The correct URL is www.hhs.gov/pharmacy/ccrf.html. On this page, select the option under responder references for dosing cards.

Human papillomavirus (HPV) vaccine review

This concise review describes the pharmacology, efficacy, safety, and cost-benefit of two new HPV vaccines: Gardasil[®], which is already available, and Cervarix[®], which is awaiting FDA approval. While both vaccines appear to be effective against the most common viral types, there are distinct differences between the two products. In addition to comparing the two vaccines, the authors comment on the need for additional research to optimize their use. Schmiedeskamp MR, Kockler DR. Human

papillomavirus vaccine. *Ann Pharmacother* 2006;40:1344-52.

Morphine pharmacokinetics in ECMO

Fourteen neonates were enrolled in an observational study to define the metabolism of morphine during venoarterial extracorporeal membrane oxygenation (ECMO). Morphine-3-glucuronide was the predominant metabolite measured. Metabolite clearance rates were lower in ECMO patients than in historical controls (infants receiving morphine after non-cardiac surgery) during the first 10 days. Higher ECMO flow rates were associated with reduced clearance rates, possibly reflecting the increased severity of illness in patients requiring greater ECMO support. The slower clearance of morphine-3-glucuronide was attributed to reduced renal clearance and correlated with creatinine clearance. Peters JWB, Anderson BJ, Simons SHP, et al. Morphine metabolite pharmacokinetics during venoarterial extra corporeal membrane oxygenation in neonates. *Clin Pharmacokinet* 2006;45:705-14.

Pediatric licensing status

It is well known that most drugs entering the market in the United States are initially approved by the FDA only for use in adults. Many, however, eventually gain additional approval for use in children. The authors of this paper reviewed the pediatric licensing status of drugs approved between 1998 and 2002. At the time of initial FDA approval, only five of the 133 drugs licensed (4%) had a pediatric indication. By the end of three years of marketing; however, this number had increased to 39 (29%). In addition, 79 of the drugs (59%) were available in a dosage formulation appropriate for children. Although the number of drugs approved for children increased substantially during the years studied, the authors point out that the majority of approvals were for children over 6 years of age and that more emphasis may be needed on the medication needs of younger children. Balakrishnan K, Grieve J, Tordoff J, et al. Pediatric licensing status and the availability of suitable formulations for new medical entities approved in the United States between 1998 and 2002. *J Clin Pharmacol* 2006;46:1038-43.

Rasburicase for tumor lysis syndrome in neonates

Rasburicase, recombinant urate oxidase, has been shown to be effective in preventing tumor lysis syndrome in children and adults receiving chemotherapy for a variety of cancer types. It has not been studied in the neonatal population. The authors of this report describe the use of rasburicase in two patients: a 3-week-old with neuroblastoma and a newborn with acute

lymphoblastic leukemia. The first patient developed symptoms of tumor lysis syndrome after 2 days of induction chemotherapy. She received a single dose of rasburicase (0.2 mg/kg IV) with subsequent normalization of serum urate levels. The second patient developed spontaneous tumor lysis syndrome with renal dysfunction. Administration of six doses of rasburicase (two doses of 0.1 mg/kg and four doses of 0.2 mg/kg) failed to halt the progression of the syndrome and the patient subsequently died of cardiopulmonary failure and electrolyte abnormalities. The authors suggest that, while rasburicase appeared to effectively lower serum urate levels, it may not be adequate to alter the progression of severe tumor lysis syndrome. McNutt DM, Holdsworth MT, Wong C, et al. Rasburicase for the management of tumor lysis syndrome in neonates. **Ann Pharmacother** 2006;40:1445-50.

Remifentanyl use in infants

The authors of this review describe the current experience with remifentanyl, a short-acting synthetic opioid, in neonates and infants. Remifentanyl offers the advantages of a short half-life and a pharmacokinetic profile that is not altered in patients with renal or hepatic dysfunction. The article includes information on pharmacokinetics and dynamics, as well as clinical reports of remifentanyl use as an anesthetic, during mechanical ventilation, and for procedural sedation. Welzing L, Roth B. Experience with remifentanyl in neonates and infants. **Drugs** 2006;66:1339-50.

Treatment of lupus nephritis

This article reviews the current drug therapy approaches to the management of lupus nephritis in children. The authors address standard treatments, including corticosteroids and other traditional immunosuppressive therapies, as well as newer treatment options and several investigational agents. A treatment algorithm is included, making this article a useful reference for new practitioners. Adams A, MacDermott EJ, Lehman TJA. Pharmacotherapy of lupus nephritis in children: a recommended treatment approach. **Drugs** 2006;66:1191-207.

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 8/24/06:

1. Ibuprofen lysine injection (Neoprofen[®]) was added to the Inpatient Formulary as an

alternative to indomethacin for closure of patent ductus arteriosus. It is given as a three dose series, with a 10 mg/kg initial dose followed by two doses of 5 mg/kg administered at 24 and 48 hours after the first dose. As with indomethacin, patients must be monitored for impairment of renal function throughout treatment.

2. Ranibizumab (Lucentis[®]) was added to the Inpatient Formulary for the treatment of macular degeneration.

3. Zileuton (Zyflo[®]) was added to the Formulary for use as an adjunct therapy in the aspirin desensitization protocol for patients with chronic asthma.

4. Human papillomavirus (HPV) vaccine (Gardasil[®]) was added to the Outpatient Formulary. This vaccine is currently recommended for females between 9 and 26 years of age for the prevention of disease caused by HPV strains 6, 11, 16, and 18. The ACIP recommends routine immunization of girls at 11-12 years of age. The HPV vaccine has been added to the Vaccines for Children program.

5. Rotavirus vaccine (RotaTeq[®]) was added to the Outpatient Formulary for children between 6 and 32 weeks of age.

6. Zoster vaccine, live (Zostavax[®]) was added to the Outpatient Formulary for the prevention of herpes zoster infection (shingles) in patients 60 years of age and older.

7. Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (Atripla[™]) was added to both the Inpatient and Outpatient Formularies for the management of patients with HIV infection.

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